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Naltrexone for Opioid Use Disorders: A Review of Clinical Effectiveness, Cost-Effectiveness, and Guidelines

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Context and Policy Issues

Illicit or licit use of prescription painkillers, heroin, or other similar substances can lead to dependence on the class of drugs known as 'opioids'. These drugs act on opioid receptors in the body to produce effects similar to morphine. In Canada, the overall usage of prescription opioids has doubled in the past 10 years, as has the number of people in Ontario seeking treatment for opioid dependence. There were an estimated 200,000 people with prescription opioid dependence in 2012.[1]

The addictive nature and the severity of the withdrawal symptoms limit people's ability to address their dependence without help. Classic withdrawal symptoms drug craving, anxiety, restlessness, diarrhea, diaphoresis, and tachycardia.[2] Clinically-assisted treatments are thus available to help people curb their dependence and to prevent relapse.[3] To help ensure safe and successful withdrawal, opioid agonists such as methadone and buprenorphine (a partial agonist) bind to opioid receptors to produce their own biological response that blocks the response created by other opioids. These treatments effectively substitute a 'worse' opioid for a longer-lasting 'better' one so that the person experiences a lesser rush of euphoria while withdrawal symptoms and cravings are controlled.[4]

After initial withdrawal, opioid antagonists can be administered to continue to ease the transition and prevent relapse. In contrast to the opioid agonists mentioned above, antagonists such as naltrexone are not opioids and do not create their own response. They instead block the effects of opioids if used. Naltrexone is considered a maintenance treatment because it is typically administered once the person is able to complete a short period of abstinence, to avoid precipitating a severe withdrawal. A 'successful' withdrawal is sometimes measured in terms of induction into naltrexone.[2]

In Canada, access to opioid agonists and antagonists to treat opioid use disorder varies. Currently methadone, buprenorphine and oral naltrexone are available, though physician access is regulated to various extents. Recently, an extended release injectable form of naltrexone (XR-NTX) has come to market (brand name Vivitrol). In contrast to the oral form which may require daily or twice weekly administration,[5] XR-NTX is novel because one intramuscular injection every 28 days blocks the opioid response, potentially lessening the high attrition seen with oral naltrexone.[5] However a drawback is that XR-NTX is significantly more expensive than oral naltrexone.[6]

The Food and Drug Administration in the U.S. approved XR-NTX in 2010,[7] however, in Canada extended-release naltrexone is only available through the Health Canada's Special Access Programme or for research.[8] Given the relative novelty of XR-NTX, its effectiveness compared with oral naltrexone remains unclear, despite the potential for higher adherence. In addition, the clinical and cost effectiveness of both these options is relevant because having multiple treatment options can support stakeholders to treat opioid dependence. This review assesses the clinical effectiveness, cost-effectiveness and guidelines for oral and injectable naltrexone to treat opioid dependence to inform policy-making in Canada to address the increasing burden of opioid use disorders.

Research Questions

1. What is the clinical effectiveness of naltrexone formulations for the treatment of patients with opioid use disorders?
2. What is the cost-effectiveness of naltrexone formulations for the treatment of patients with opioid use disorders?
3. What are the evidence-based guidelines associated with naltrexone formulations for the treatment of patients with opioid use disorders?

Key Findings

Extended release injectable naltrexone (XR-NTX) was favoured relative to placebo, treatment as usual or buprenorphine for abstinence duration and treatment retention outcomes. Oral naltrexone was not generally found to improve the duration of abstinence, though may be helpful to assist in induction onto XR-NTX. Safety outcomes were not found to be different among treatment versus comparator groups.

The balance of evidence suggests XR-NTX may be cost-effective relative to methadone and buprenorphine treatment depending on the willingness-to-pay. The cost-effectiveness of oral naltrexone and buprenorphine treatments was similar on almost all primary outcomes.

Guidelines generally recommended naltrexone if other treatments were contraindicated, or if patients had demonstrated sustained abstinence. Guidelines published since 2015 specifically do not recommend oral naltrexone, but XR-NTX was recommended if adherence issues were a concern or if agonist treatment could not be used.

Methods

Literature Search Methods

A limited literature search was conducted on key resources including PubMed, The Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, ECRI, Canadian and major international health technology agencies, as well as a focused Internet search. Filters were applied to limit the retrieval to health technology assessments, systematic reviews, meta analyses, economic studies, non-randomized studies, randomized controlled trials, and guidelines. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2009 and June 2, 2017.

Rapid Response reports are organized so that the evidence for each research question is presented separately.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Any patient with diagnosed or self-reported opioid use disorder.
Intervention	Oral or injectable naltrexone
Comparator	Q1 & Q2: Psychological, active, or placebo interventions Q3: No comparator
Outcomes	Q1: Clinical effectiveness, patient satisfaction, adherence/compliance with therapy), safety (e.g., safety when the drug is taken with opioids, opioid overdose), etc. Q2: Cost-effectiveness Q3: Guidelines
Study Designs	Health Technology Assessments, Systematic Reviews, Randomized Controlled Trials, Evidence-based Guidelines

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published prior to 2009. Studies where the naltrexone intervention was investigated in populations that were not opioid users (for example, subjects dependent on alcohol), or where the intervention was naltrexone implants only were excluded.

Critical Appraisal of Individual Studies

The included systematic reviews were critically appraised using the AMSTAR checklist,[9] randomized studies were critically appraised using the Downs and Black checklist,[10] economic studies were assessed using the Drummond checklist,[11] and guidelines were assessed with the AGREE II instrument.[12] Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 378 citations were identified in the literature search. Following screening of titles and abstracts, 332 citations were excluded and 46 potentially relevant reports from the electronic search were retrieved for full-text review. Four potentially relevant publications were retrieved from the grey literature search. Of these potentially relevant articles, 27 publications were excluded for various reasons, while 23 publications met the inclusion criteria and were included in this report. Appendix 1 describes the PRISMA flowchart of the study selection.

Summary of Study Characteristics

Details of the individual study characteristics are provided in Appendix 2.

Study Design

Ten randomized controlled trials[13-22] and four systematic reviews were included in the review.[23-26] Two of the trials were pilot/proof-of-concept studies.[18,19] One study[14] was a

secondary analysis of data from a trial that was also included in this report.[13] Three of the systematic reviews included both randomized controlled trials and observational studies, and included two,[23] six[24] and four[25] studies of naltrexone respectively. The last systematic review included thirteen randomized or controlled clinical trials on oral naltrexone.[26] The most recent systematic review included publications until December 2016,[24] while the others included literature up to December 2009,[25] June 2010,[26] and September 2009.[23]

Two cost-effectiveness studies reported on costs based on randomized controlled trials,[6,27] while one reported costs based on a retrospective cohort analysis of administrative data.[28] The last study used a Markov model to ascertain cost-effectiveness comparing XR-NTX to any active comparator in adult males starting pharmacotherapy for opioid dependence, with a time horizon of six months. The main assumptions included flexible medication dosing based on best clinical practice, and that the off-treatment probability of abstinence and the death rate were constant.[29]

The guidelines were developed on the basis of existing systematic reviews and other guidelines with supplementation through their own evidence reviews and/or meta-analyses,[30-32] or initiated their own systematic reviews of evidence to draft the recommendations.[33] One guideline did not provide detail other than to say a structured literature review was conducted.[8]

In addition to evidence collection, all the guidelines' development process involved having an expert committee to reach consensus. Two guidelines stated established methods for development including adherence to the AGREE II protocol[8] and the RAND/UCLA Appropriateness Method to reach consensus.[30] The guidelines were all developed iteratively with opportunities for feedback from other stakeholders before finalization.

Country of Origin

Two clinical trials were conducted in Russia,[13,14] one was conducted in the Republic of Georgia,[20] and one was conducted in Iran.[15] The remainder were conducted in the U.S.[16-19,21,22] The systematic reviews did not have geographic restrictions.

Three cost studies were U.S. based.[6,28,29] One did not specify a perspective,[28] but the other two were from the perspective of U.S. state addiction treatment payers,[29] and the other was from the U.S. taxpayer perspective.[6] The last study was based in Malaysia, and was from the provider and societal perspectives.[27]

Two guidelines retrieved were international,[31,32] from the World Health Organization[32] and The World Federation of Societies of Biological Psychiatry.[31] One was Canadian, issued by the British Columbia Centre on Substance Abuse,[8] while the two remaining were issued by the Department of Veterans Affairs[33] and the American Society of Addiction Medicine[30] in the U.S.

Patient Population

Systematic reviews

All systematic reviews included studies with participants dependent on or withdrawing from heroin, with two studies explicitly including those who were currently on methadone, if they were former heroin users.[24,26]

Randomized studies

All studies except one required participants to have an opioid dependency that met the Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV or DSM-V criteria; the remaining study required a diagnosis of opioid dependence but did not specify the criteria.[14] No study included children or adolescents under 18. The study populations were predominantly male, whether or not this was specified in the inclusion criteria. One study explicitly restricted to male participants.[20] Six studies included either an inpatient or outpatient withdrawal procedure involving opioid agonists prior to randomization[13-16,20,21] while four other studies only randomized upon determining opioid-free status through urine tests.[17-19,22] The primary opioid dependence in all studies but one was heroin, with the remaining study's participants' primary substance of misuse was buprenorphine, which reflected the broader opioid context in the Republic of Georgia.[20]

The most common exclusion criteria were related to pregnancy/breast-feeding[13,14,16-19,22] abnormal liver function tests,[13-16,19,22,24] an indication for prescription opioids for chronic pain,[18,19,21,22] or other substance dependencies.[13-17,19,21] Eight studies also explicitly excluded people with severe mental health issues or impaired cognitive functioning,[13-17,19,20,22] and five studies explicitly required good general health.[16-19,22] Two studies excluded people with a history of accidental opioid overdose.[19,21]

One study specifically recruited HIV-infected participants,[18] though other studies did not specifically exclude these populations. Four studies included only participants involved with the criminal justice system.[17-19,22] The latter four studies of criminal offenders were the same ones that did not provide detoxification as part of the study prior to randomization to naltrexone; incarceration provides a form of forced detoxification.

Three studies required having a female partner, spouse or relative to help supervise compliance[13,14,20] with one further specifying that the partner needed to be a "drug-free female sexual partner with whom they had regular contact,"(pg 3).[20]

Cost studies

Similar to the clinical studies, the cost-effectiveness studies were restricted to adult opioid-dependent populations. One study additionally required the opioid-dependent adults to have been involved with the criminal justice system, thus focusing on cost-effectiveness among criminal offenders.[6] Another restricted its population to insured patients in the U.S. due to the use of administrative data,[28] and the Malaysian study required patients to have completed a 14-day residential protocol for opioid addiction.[27]

Guidelines

All of the guidelines targeted practitioners or other professionals involved in the care of adults with opioid dependence or opioid use disorder. One U.S. guideline additionally stated medical educators and clinical care managers as a target audience of the guidelines,[30] while the World Health Organization guidelines also targeted health systems and health system managers.[32]

Interventions and Comparators

Systematic reviews

Two studies focused on naltrexone only as the intervention, one of which considered oral naltrexone[26] and the other considered depot (injectable) naltrexone.[25] The remaining two

studies included a broader range of interventions, at least one of which involved a naltrexone formulation.[23,24] The comparators included other pharmacological or psychosocial treatment,[24,26] placebo,[25,26] having no comparator,[25] or any comparator.[23]

Randomized studies

The intervention in three studies was daily or every-other-day 50mg oral naltrexone,[15,17,20] while six other studies used 380mg XR-NTX administered once every four weeks.[13,14,18,19,22] One study randomized to low dose (192 mg) and high dose (384 mg) XR-NTX,[16] while another involved increasing daily doses of oral naltrexone (starting at 1mg on day 4 until 25 mg at day 8), followed by XR-NTX on day 9.[21] Counselling was generally offered alongside the main intervention and comparator; however one study included an extensive counselling program involving inpatient detoxification, partner support and therapy, and financial incentives that were not available to the comparator group.[20]

Treatment as usual, agonist therapy, and placebo were the three types of comparators used across the studies. Five studies used treatment as usual depending on the local standard of care.[17-20,22] This consisted of counselling sessions, referrals to non-intervention treatment if requested, education sessions[17-20,22], and buprenorphine/naloxone in some patients when indicated.[18]. Two studies administered buprenorphine-based regimens to the comparator group.[15,21] Of these, one administered buprenorphine in decreasing daily doses from days 2 to 7 of treatment, followed by a 7-day washout period before giving the comparator group XR-NTX as well,[21] while the other administered 8mg buprenorphine/naloxone tablets.[15] The remaining three studies compared the intervention to placebo.[13,14,16]

Cost studies

The intervention in three studies was XR-NTX alone,[6,28,29] with one study explicitly stating exclusion of oral naltrexone due to a previous finding of inferiority against methadone or buprenorphine maintenance treatment.[29] The remaining study used oral naltrexone as the intervention.[27]

The comparators varied across the studies. Two studies compared interventions including buprenorphine, with one additionally including ‘no medication’ and methadone comparators,[28] and the other additionally including a placebo comparator.[27] Another U.S. study included any comparator except placebo and non-pharmaceutical treatments,[29] and the last study included only treatment as usual (i.e. counselling and referral to medical treatment as requested).[6]

Guidelines

Each guideline reviewed several interventions for treating opioid dependence, with naltrexone highlighted as a smaller part of a larger and more comprehensive guideline. Three guidelines focused on pharmacological agents and medications,[30-32] while two were broader in their focus including psychosocial or other non- pharmacological interventions.[8,33] All the guidelines considered naltrexone, to varying degrees, and had at least one recommendation with mention of either oral naltrexone and/or XR-NTX.

Outcomes

Systematic reviews

Three reviews considered abstinence, relapse, and duration of treatment,[24-26] while two also considered adverse events or safety/tolerability.[24,25] Heroin craving[23] and the severity of withdrawal syndrome[24] were also measured in two reviews.

Randomized studies

The primary outcome in seven studies related to positive/negative urine samples indicating opioid relapse, time to opioid relapse, or duration of abstinence as measured through urine toxicology and self-report.[13,15-17,19,20,22] Three studies assessed initiation of treatment (i.e. induction onto XR-NTX or receipt of at least one treatment dose within 4 weeks of randomization),[18,20,21] two assessed retention,[16,18] and one measured safety outcomes including liver enzyme levels.[14] One study additionally measured criminal charges in a population of criminal offenders[17] and another measured drug risk behaviours as primary outcomes.[20]

Cost studies

A variety of outcomes both within and across studies were considered which are listed in Appendix 4. The primary costs considered were the cost of drugs and medical care visits. Two studies were broader as they also covered costs such as emergency department visits, mental health sessions and criminal justice related costs,[6] and facilities, travel and family's time.[27] The outcomes related to overall healthcare cost[28] and incremental cost-effectiveness ratios to assess the cost of an additional opioid-free day,[27,29] abstinent-year,[6] or an additional unit of outcome achieved such as percent reporting injection drug use and employment.[27]

Guidelines

One guideline explicitly stated outcomes of interest a priori,[33] which included time to relapse, adherence with treatment or abstinence, retention/engagement in the treatment program, number lost to treatment, adverse events, morbidity, mortality, overdoses, hospitalization, emergency department visits and healthcare utilization. This guideline also included recovery outcomes such as quality of life. The other guidelines did not state clear a priori outcomes, but reported on the outcome measures that were used in the studies upon which they based the recommendations. The recommendations pertained to the same measures listed above.[8,30-32]

Summary of Critical Appraisal

Details of the critical appraisal of individual studies are described in Appendix 3.

Systematic reviews

Two systematic reviews were considered higher quality as they included a risk of bias assessment for individual papers and a comprehensive literature search that involved several databases. One of these employed three reviewers to scan titles and abstracts, and two to extract data, and additionally discussed the potential for publication bias.[26] Additionally, this study employed random effects models to handle heterogeneity across studies, and downgraded overall quality ratings when heterogeneity was considered high. The other lacked a second reviewer and did not mention publication bias, though stated

that all authors confirmed inclusion and exclusion of articles and assessed heterogeneity across studies using I^2 The results were not pooled.[24]

The other two systematic reviews were less strong. One was limited to one database, did not contain a critical appraisal or detail on extraction procedures, including whether two reviewers were involved.[23] The other included seven databases and independent screening by two authors, but lacked detail on a specific research question (i.e. PICO), study characteristics, critical appraisal, and did not search grey literature.[25]

Randomized studies

The quality of the randomized controlled trials was variable. The four double-blinded studies were generally of good quality,[13-16] but three did not provide adequate detail on procedures.[14-16] Two studies lacked detail to adequately judge allocation concealment and randomization procedures,[15,16] and two of these studies did not provide a table of characteristics to judge whether baseline statistics were similar between groups.[14,16] Among these four studies, one study excluded patients with abnormal liver function despite a stated objective to assess safety among patients with liver disease.[14] In addition, another of the double-blinded studies did not provide a typical flow chart to assess the evolution of the sample sizes across arms.[16] One study specified the exact parties that were blinded.[13] While this study was deemed the strongest due to its detailed description of procedures, independent statistical analysis, and successful randomization, one limitation was that the sponsor, i.e. the XR-NTX manufacturer Alkermes, designed and managed the study, and collected and analysed the data.

The rest of the randomized studies were first limited by employing open-label treatments. They also generally failed to provide enough detail to adequately judge randomization and allocation concealment. Three of the studies had low follow up rates,[17,20,22] for instance, 43% of assessments were missing in one study.[20] Three were also underpowered or conducted analyses only using sparse data.[17,18,20] At the same time, strengths of these studies included appropriate statistical analyses and generally balanced baseline characteristics between treatment groups, and two used imputation techniques to speculate the impact of missing data.[17,22] While most studies defined the interventions clearly, the exception was two studies where differences in regimens administered to the intervention and comparator groups were extensive enough that it may not be possible to attribute any effect to naltrexone.[20,21]

Cost studies

Three of the studies were each based on one randomized trial,[6,27,29] while the other was limited to data from an insurance claims database potentially affecting generalizability.[28] The insurance claims database study used a retrospective cohort design including 14 million people to identify those with a diagnosed opioid dependence. It included data from 2005 to 2009, and derived costs from patient claims, however there was no clear measure of effectiveness and a limited viewpoint of costs that could be assessed through administrative claims.[28]

Two studies estimated costs directly rather than using the Markov modelling techniques typically used for cost-effectiveness analyses.[6,27] Due to this design, the stated assumptions were limited, but would align with the generalizability of the primary studies which included a criminal offender population[6] and patients who completed a 14-day residential protocol.[27] One of these studies costed drugs only based on public sector

pricing, used mean annual salaries to estimate the cost of medical management visits despite the potential for regional variation, and lacked sensitivity analyses.[6]

The last study employed a Markov model to estimate the incremental cost-effectiveness ratio for XR-NTX, considering only competing alternatives with a state-insurance payer viewpoint that is relevant for decision making. The study conducted sensitivity analyses to determine which variables most affected the cost-effectiveness and considered several costs such as drug, counselling, reimbursements for pharmaceuticals, though no costs outside of those directly related to healthcare were considered.[29] The transition probabilities were based on a clinical trial that was also included in this review. The time horizon of six months aligned with the clinical trial on which the study was based.[13] One assumption of a constant probability of relapse when off-treatment may be questionable if we expect the risk to change with time, though the assumption was justified through previous literature.

The Malaysian study considered a wide range of costs, including societal and healthcare/provider costs,[6] while the others were restricted to costs that were directly associated with healthcare and treatment provision; they did not consider costs from a societal perspective.[6,28,29]

Guidelines

The five guidelines were all considered high quality and had similar strengths and limitations. The strengths of the guidelines included clearly stated scope and purpose and the collection of evidence from systematic reviews and clinical trials. Each guideline judged the quality of evidence, using GRADE criteria in three cases[8,32,33] or an internal evaluation scheme.[30,31] One guideline provided detail on the systematic review methods, specifying their inclusion/exclusion criteria and highlighting that they reviewed 4708 citations and included 135 RCTs/systematic reviews.[33] The remaining guidelines did not provide enough detail to evaluate the quality of the their evidence collection methods.

The recommendations were based on evidence as well as consultation with expert panels and opportunities for feedback from independent stakeholders. Two guidelines followed formal approaches to development, including RAND-UCLA[30] and AGREE II.[8] Another guideline[33] followed an internal formal methodology to developing guidelines that was in a separate published document on the website.[34] A common limitation across all the guidelines was lack of patient involvement and clear validation procedures.

Summary of Findings

Details of individual study findings are presented in Appendix 4.

What is the clinical effectiveness of naltrexone formulations for the treatment of patients with opioid use disorders?

For treatment completion, attendance or retention, five of six clinical studies assessing these outcomes favoured oral naltrexone (n = 1) or XR-NTX (n = 4) relative to comparators.[13-16,18] One study did not find a difference in oral naltrexone versus treatment as usual for treatment completion,[17] Two studies found higher rates of weekly negative urine samples in the intervention oral naltrexone versus control group (19.7 vs 15.4 $p = 0.049$[15], and 7.0 vs 1.4; $p < 0.001$[20]), though one study did not find a difference in this rate in oral naltrexone versus treatment as usual.[17]

The likelihood of initiating XR-NTX was found to be lower compared to the likelihood of initiating usual care (42% vs 100% initiated),[18] but when rapid oral naltrexone-assisted

detoxification was compared to slow taper bupropherine detoxification to induct onto XR-NTX, the naltrexone regime was favoured (odds ratio [OR] 2.89, p = 0.04).[21] Another study also favoured oral naltrexone compared to usual treatment for entrance to detoxification and further naltrexone treatment (0% vs 50% and 0% vs 60%, respectively).[20] At the same time, naltrexone was not found to improve heroin cravings,[23] and was associated with a possibility of delirium on the first day, especially with a dose of more than 25mg.[24] It was unclear whether peak or average withdrawal severity was worse compared to clonidine or lofexidine alone.[24]

In terms of opioid abstinence outcomes, XR-NTX was generally favoured against its comparators while oral naltrexone was not. One study found a lower risk of relapse among XR-NTX-assigned patients compared to treatment as usual, including counselling and referrals to community-based methadone/buprenorphine as requested (hazard ratio [HR] 0.49; 95% confidence interval [CI] 0.36 to 0.68, p < 0.001) but the effect did not persist to week 78.[19] A pilot trial for the same study[22] favoured XR-NTX (OR 0.08; 95% CI 0.01 to 0.48, p <0.004), and 55% more weeks with confirmed abstinence among the XR-NTX group compared to placebo was also found in another trial.[13] This last study also found a clinical response among placebo participants, though the benefit was less than in the treatment group. Sustained release formulation users including both injection and implant were also found to use less opioids compared to placebo/no comparator groups in a systematic review; the study highlights “optimism” (pg 632) based on several small studies with regard to injectable naltrexone specifically, though there was a general lack of larger studies on injectable naltrexone.[25] At the same time, there was no difference in opioid abstinence outcomes in oral naltrexone versus buprenorphine/naloxone groups in the other trial assessing this outcome,[15] as well as in a systematic review comparing oral naltrexone vs other pharmacologic treatments.[26]

Safety outcomes and adverse events were found to be the same across treatment and comparator groups in the clinical studies, including liver chemistry, the need for protective transfer, deaths from overdose, aggression/violence, withdrawal symptoms and/or insomnia.[13-15,21,26] One systematic review warned of the possibility of nausea, vomiting and muscle twitches, and injection-site reactions associated with naltrexone.[25]

What is the cost-effectiveness of naltrexone formulations for the treatment of patients with opioid use disorders?

A study based on healthcare claims found that the overall healthcare cost of XR-NTX was higher than that of methadone ($16,752 vs $8,582, respectively), but overall healthcare costs were similar to costs associated with buprenorphine maintenance treatment.[28] A Malaysian study also found that buprenorphine was more costly, but also more effective than oral naltrexone, for outcomes relating to the cost per additional day in treatment,[27] though most of the incremental cost-effectiveness ratios were below $50. However for secondary outcomes which were more removed from direct treatment effects, for example AIDS risk scores, use of other illicit opiates and earnings, naltrexone was dominated by placebo for most (i.e. naltrexone was more costly and less effective).[27] Another study found the incremental cost-effectiveness ratio of injectable naltrexone was $72 per opioid free day relative to methadone maintenance treatment.[29] The final study, which focused on a criminal offender population, found that the cost per abstinent year for XR-NTX versus treatment as usual (counselling and community referrals) was $16,371 and the cost per QALY was $76,400 at 78 weeks, though there was no difference in cost associated with criminal justice resource utilization compared to treatment as usual.[6]

What are the evidence-based guidelines associated with naltrexone formulations for the treatment of patients with opioid use disorders?

There were few specific recommendations pertaining to naltrexone, and the timeline of the guidelines is relevant since XR-NTX was approved in the U.S. in 2010 and there lacked studies until more recently, preventing guidelines developed around this time from having enough evidence to make recommendations on XR-NTX.

Two guidelines developed in 2009 and 2011 do not recommend naltrexone. The World Health Organization guidelines[32] suggest that while naltrexone treatment could be offered, most patients should use agonist maintenance treatment. The alternative, based on low quality evidence, could be naltrexone once withdrawal is complete.[32] Similarly, a 2011 guideline recommended against using oral naltrexone as a first line treatment for opioid dependency, though it is a potential treatment among a select group of patients, though retention is poor. The guideline does comment that injectable naltrexone had just become approved and available in the U.S. but point to a lack of studies to base recommendations.[31]

More recent guidelines (published 2015 or later) conclude that oral naltrexone cannot be recommended for treatment but XR-NTX could be considered in those where agonists are contra-indicated.[33] Another recent guideline also recommends that oral naltrexone should only be used with particularly highly motivated patients, and suggests that the compliance issue is reduced but not eliminated with XR-NTX.[30] However, naltrexone is the recommended treatment to prevent relapse, and XR-NTX specifically when adherence issues are a concern, with no recommended length for treatment duration.[30] The exception is the British Columbia guideline which recommends that a transition to oral naltrexone could be considered upon cessation of opioids, though they do not comment on XR-NTX specifically.[8]

Limitations

In all clinical studies included in this review, patients were managed extensively, for example twice a week,[16] and had access to several counselling, outpatient or inpatient resources which may limit generalizability, depending on the resources to do this type of follow up in a real world setting. There was also generally limited reporting of safety outcomes and adverse events, including the risk of overdose upon relapse due to de-sensitizing of opioid receptors, which may have been because of relatively short follow up periods or the failure to track down those lost to follow up. The primary drug of choice across all studies was heroin, so generalizability beyond heroin users is unclear. In addition, no studies compared XR-NTX to oral naltrexone which would be of interest. The two systematic reviews that appraised their studies found them to be of mixed quality due to poor descriptions of randomization and allocation concealment procedures,[26] or of very low quality[24] due to risk of bias, results inconsistency, study size, or no randomization.

Cost-effectiveness studies were mainly limited by a general lack of primary studies upon which to base their models, including transition probabilities. The context of three of the studies that were conducted also may not be generalizable to Canada as one study was Malaysian,[27] the other was among criminal offenders specifically,[6] and the third study included insured U.S. patients.[28] In the final study the target was U.S. males, but there was not a restriction that would preclude generalizability beyond U.S. males.

There lacked guidelines that specifically focused on XR-NTX; they were instead broader and considered most pharmacologic or other treatments for opioid use disorders. While all but one[8] do mention XR-NTX, as is similar to the cost-effectiveness literature, the general lack of guidance on XR-NTX may stem from the lack of primary studies available at the time of guideline production.

Conclusions and Implications for Decision or Policy Making

XR-NTX was generally favoured against comparators including placebo, treatment as usual or buprenorphine to improve treatment completion, attendance or retention, as well as the duration of abstinence in the short term. One study demonstrated this effect was not sustained at 78 weeks.[19] Oral naltrexone was not found to improve duration of abstinence, and was found to have a high overall study dropout rate. However, one study found oral naltrexone favourable compared to buprenorphine to assist in induction onto XR-NTX.[21] Overall, safety outcomes were similar across all treatment and comparator groups.

While XR-NTX came across as favourable in these studies, policy-makers should be aware that the primary drug of choice across all studies was heroin, and the best quality trial was conducted in Russia and run by the drug manufacturer Alkermes.[13]

The balance of evidence suggests XR-NTX may be cost-effective depending on the comparator and willingness-to-pay, and no difference in cost-effectiveness was reported for oral naltrexone versus buprenorphine. Overall healthcare cost may be less for XR-NTX relative to methadone maintenance treatment[28] but not relative to treatment as usual even though there was less use of therapy and health care services among XR-NTX patients.[6] One study found XR-NTX is cost-effective compared to methadone and buprenorphine maintenance treatments, assuming a willingness-to-pay threshold of $72/opioid-free day-gained.[29] The one study assessing oral naltrexone in Malaysia found oral naltrexone and buprenorphine treatments were similar on almost all primary outcomes.[27] There were limitations posed by the lack of primary studies upon which these cost-effectiveness analyses were based, and the potential lack of generalizability to Canada.

The guidelines generally only recommended naltrexone if other treatments were contraindicated, or if patients demonstrated sustained abstinence and high motivation. Guidelines published after 2015 specifically do not recommend oral naltrexone, but XR-NTX was recommended if adherence issues were a concern or if agonist treatment could not be used.[30,33] A limited number of studies specifically focusing on XR-TNX were considered for these guidelines, which in term may have affected the strength of recommendations on this intervention.

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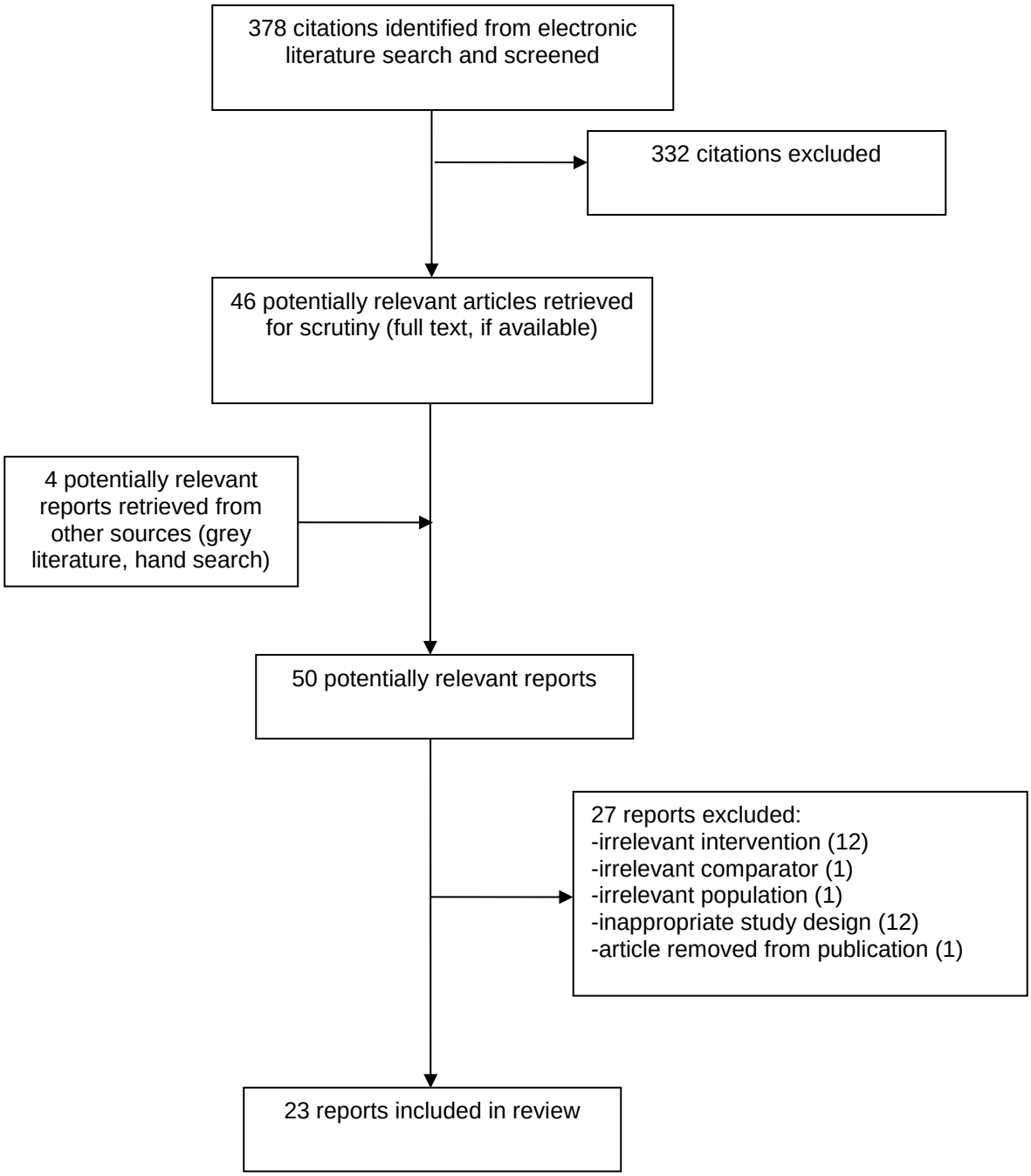
Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 1: Characteristics of Included Systematic Reviews

First Author, Publication Year	Types and numbers of primary studies included	Population Characteristics	Intervention	Comparator(s)	Clinical Outcomes
Fareed, 2010[23]	Included 12 randomized controlled trials and observational studies, but only 2 on naltrexone	Unspecified, but intervention had to be among heroin users	Opiate agonist, antagonist, dopamine receptor antagonist and other experimental medications	Any	Severity of heroin craving
Gowing, 2017[24]	Included 10 RCTs (n=6) and prospective controlled cohort studies (n=3), of which 6 used a treatment regimen based on naltrexone	Unspecified, but in 6 studies, participants were withdrawing from heroin, and in the other 4 studies participations were using heroin, methadone or both	Naltrexone administration in the first three days of treatment or within three days of last opioid use	Tapered doses of methadone, buprenorphine, symptomatic medications or placebo, or antagonist-based regimens differing in the type or dose regimen of opioid antagonist.	Severity of withdrawal syndrome, duration of treatment, adverse effects and treatment completion
Lobmaier, 2011[25]	Included 46 studies, of which, 4 of which were on naltrexone injections (1 was an RCT, 3 studied safety and tolerability)	Opioid-dependent (no further detail provided)	Naltrexone depot or implant treatment	Placebo or none	Safety and tolerability outcomes, and heroin relapse rates
Minozzi, 2011[26]	13 randomized controlled trials or controlled clinical trials	Patients currently dependent on heroin, or formerly dependent on heroin but currently dependent on methadone who are participating in a naltrexone treatment programme	Oral naltrexone	Placebo or other pharmacological/psychosocial treatment to prevent relapse	Abstinence of heroin use

Table 2: Characteristics of Included Clinical Studies

First Author, Year, Country, Title	Study Design	Patient Characteristics	Intervention(s)	Comparator(s)	Clinical Outcomes
Coviello, 2010, U.S., "A Randomized Trial of Oral Naltrexone for Treating Opioid-Dependent Offenders"[17]	RCT	Opioid-dependent (heroin) criminal offenders	Oral naltrexone plus standard psychosocial treatment	Treatment as usual (standard psychosocial treatment without naltrexone)	-Opioid positive urines -Committing crime -Adherence to six-month treatment protocol
Korthuis, 2017, USA, "Feasibility and safety of extended-release naltrexone treatment of opioid and alcohol use disorder in HIV clinics: a pilot/feasibility randomized trial"[18]	RCT	HIV-infected participants undergoing HIV care at the study sites, who met criteria for opioid use disorder	XR-NTX 380mg injected by clinician at treatment initiation and at 4, 8 and 12 weeks (16 weeks exposure)	Treatment as usual (local standard of care; primarily buprenorphine/naloxone)	Acceptance of treatment, recruitment rate, treatment initiation and retention
Krupitsky, 2011, Russia, "Injectable extended-release naltrexone for opioid dependence: a double-blind, placebo-controlled, multicentre randomised trial"[13]	RCT	Men and women aged 18+ with opioid dependence, who were undergoing inpatient opioid detoxification, and off opioids for at least 7 days	380 mg XR-NTX every 4 weeks up to 24 weeks (total 6 injections) with counselling sessions	Placebo injection every 4 weeks up to 24 weeks (total 6 injections) with counselling sessions	Response profile for abstinence weeks 5-24
Lee, 2015, U.S. "Opioid treatment at release from jail using extended release naltrexone: a pilot proof-of-concept randomized effectiveness trial"[22]	RCT	Opioid-dependent adults aged 18+ incarcerated in New York City Department of Corrections jails with a known release date	XR-NTX 380mg injected by clinician at initiation and once 4 weeks later and counselling	Treatment as usual (counselling) plus referrals to community treatment	Opioid relapse at week 4
Lee, 2016, U.S. "Extended-Release Naltrexone to Prevent Opioid Relapse in Criminal Justice Offenders"[19]	RCT	Adults aged 18-60 with current or lifetime opioid dependence, opioid-free status, desire for non-opiate treatment, who had an adjudicated sentence (e.g. parole, probation) or were released from prison/jail in the past 12 months	XR-NTX 380mg injected by clinician/nurse once every four weeks up to 24 weeks with counseling	Treatment as usual (counseling only), though buprenorphine and methadone could be indicated during the trial (referrals to community treatment)	Time to relapse, opioid-negative urine samples, proportion of 2-week intervals with no opioid use, proportion of days with opioid use
Mitchell, 2012, Russia "Hepatic Safety of Injectable Extended-Release Naltrexone in Patients With Chronic Hepatitis C	RCT	Opioid-dependent patients actively seeking treatment and had received inpatient treatment for opioid use	XR-NTX 380 mg every 4 weeks for a total of 6 injections	Placebo injection every 4 weeks up to 24 weeks (total 6 injections) with counselling sessions	-Treatment-emergent adverse events and abnormal laboratory tests -Liver enzyme

First Author, Year, Country, Title	Study Design	Patient Characteristics	Intervention(s)	Comparator(s)	Clinical Outcomes
and HIV Infection"[14]					levels
Mokri, 2016, Iran "Medical treatments for opioid use disorder in Iran: a randomized, double-blind placebo-controlled comparison of buprenorphine/ naloxone and naltrexone maintenance treatment"[15]	RCT	Opioid-dependent patients actively seeking treatment	Oral naltrexone 50 mg capsules (+ placebo Buprenorphine/Naloxone) + counselling	8mg Buprenorphine/Naloxone tablet (+ naltrexone placebo capsule) + counselling	Duration of initial opioid abstinence
Otiashvili, 2012, Georgia, "Drug Use and HIV Risk Outcomes in Opioid-Injecting Men in the Republic of Georgia: Behavioral Treatment + Naltrexone compared to Usual Care"[20]	RCT	Opioid-dependent men above age 18 with a current drug-free female sexual partner that they regularly contact	Individualized oral naltrexone dose, plus behavioural therapy (including couples counselling)	Usual care (outpatient, education sessions, community resources)	Entering detoxification, entering naltrexone treatment, weekly urine samples, drug risk
Sullivan, 2013, U.S. "Naltrexone treatment for opioid dependence: Does its effectiveness depend on testing the blockade?"[16]	RCT	Heroin dependent adults aged 18-59 years seeking treatment at one of two university medical centers	Low dose-192 mg or high dose-384 mg depot (injectable) naltrexone + relapse prevention therapy	Placebo + relapse prevention therapy	Retention in treatment and urine toxicology to detect opioid use
Sullivan, 2017, U.S. "Long-Acting Injectable Naltrexone Induction: A Randomized Trial of Outpatient Opioid Detoxification With Naltrexone Versus Buprenorphine"[21]	RCT	Adult outpatients aged 18-60 with current opioid dependence	Naltrexone-assisted detoxification: On Day 3 clonidine and clonazepam (which continued). On day 4, oral naltrexone 1mg started, with increasing daily doses until day 8 (25mg), then 380 mg of XR-naltrexone.	Buprenorphine-assisted detoxification: decreasing daily doses of buprenorphine (8 mg to 1mg) on days 2–7, followed by a 7-day opioid washout period, and XR-naltrexone administration on day 15	Successful XR-NTX induction and receiving a second injection at week 5

RCT = randomized controlled trial; XR-NTX = Extended-release injectable naltrexone; AST = aminotransferase; ALT =alanine aminotransferase; GGT = gamma-glutamyl aminotransferase; HIV = Human Immunodeficiency Virus;

Table 3: Characteristics of Included Cost Studies

First author, Publication Year, Country	Type of Analysis, Perspective	Intervention, Comparator	Study Population	Time Horizon	Main Assumptions
Baser, 2011, U.S.[28]	Healthcare cost and utilization based on a retrospective cohort study	XR-NTX, no medication, buprenorphine and/or methadone	Insured U.S. patients with an ICD-9 diagnosis of opioid dependence	2005 to 2009	Administrative claims capture the full cost of treatment
Jackson, 2015, U.S.[29]	Markov model to estimate incremental cost-effectiveness of XR-NTX from the perspective of state addiction treatment payers	XR-NTX, any comparator except placebo and non-pharmaceutical treatments	Adult males in the U.S. starting pharmacotherapy for opioid dependence	6 months	Retention declined "geometrically" (pg 3) and equal daily probability of being abstinent while off-treatment, flexible medication dosing based on best clinical practice, and constant death rate were constant
Murphy, 2017, U.S.[6]	Economic evaluation to estimate incremental quality of life years and incremental cost per additional year of opioid abstinence gained, from the U.S. taxpayer perspective	Receiving XR-NTX vs treatment as usual	Community-dwelling opioid-dependent participants aged 18-60 involved with the criminal justice system	25 and 78 weeks after treatment initiation	-Drug cost based on public sector pricing -Cost for medical management visits based on mean annual salary reported by Bureau of Labour Statistics
Ruger, 2012, Malaysia[27]	Cost-effectiveness analysis from the provider and societal perspective	Placebo, oral naltrexone or buprenorphine	Patients completed 14-day protocol for opioid addiction	24 weeks	Costs for participants' time estimated at minimum wage level

RCT = randomized controlled trial; XR-NTX = Extended-release injectable naltrexone; EQ-5D = EuroQol – 5 Dimensions

Table 4: Characteristics of Included Guidelines

Citation	Intended users/Target pop	Intervention and Practice Considered	Major Outcomes Considered	Evidence collection, selection and synthesis	Evidence Quality and Strength	Recommendations development and Evaluation
World Health Organization, International, 2009[32]	Health systems and practitioners managing people with opioid dependence	Medications to manage opioid dependence and withdrawal	Management of opioid dependence and withdrawal	Collected Cochrane reviews when they existed or a new review was conducted	Quality assessed using GRADE	Based on technical experts group who reviewed the systematic reviews, meta analyses and, information from other sources
Kampman, U.S.[30]	Clinicians involved in treating opioid use disorder and/or authorizing pharmacologic al treatments, as well as medical educators and clinical care managers	Medications approved by US Food and Drug Administration to treat opioid dependence	Management of opioid dependence and overdose	Reviewed and synthesized all existing clinical guidelines and conducted additional systematic review	Statements were rated based on appropriaten ess, then according to necessity	Development based on RAND/UCLA Appropriateness Method
Soyka, 2011, International[31]	Clinicians involved in diagnoses and treatment of adult patients with opioid use disorders	Pharmacological agents for treating and managing opioid use disorders	Abstinence from all opioids and illegal drugs and/or a substantial decrease in the use of opioids or illegal drugs	MEDLINE and Cochrane database, guidelines searches	Quality assessed based on evidence category	Development based on evidence, and finalized based on consensus and ranking of evidence achieved through a panel of 22 international experts
British Columbia Centre on Substance Abuse, 2017, Canada[8]	Physicians, nursing and allied health professionals, and other care providers of those with opioid use disorders	Medically-assisted withdrawal management, residential treatment, agonist and antagonist therapies, psychosocial treatment, harm reduction	Not stated a priori, but outcomes related to treatment of opioid use disorder	Structured literature review	Quality assessed using GRADE	Interdisciplinary 28-member guideline committee and external reviewers
U.S. Department of Veterans Affairs, 2015[33]	Care providers of those with opioid use disorders	Pharmaco-therapy agents for alcohol and opioid use disorder, brief	Several outcomes such as opioid consumption,	Systematic review	Evidence assessed using GRADE	Guideline for Guidelines Approach: Group of clinical experts develop guidelines (15-20

Table 4: Characteristics of Included Guidelines

Citation	Intended users/Target pop	Intervention and Practice Considered	Major Outcomes Considered	Evidence collection, selection and synthesis	Evidence Quality and Strength	Recommendations development and Evaluation
		intervention, mutual help programs, psychotherapies, medical management	time to relapse, relapse and , adherence with treatment department and utilization, side effects and function status			people) based on interpreting the evidence quality and practicality

RCT = randomized controlled trial

Appendix 3: Critical Appraisal of Included Publications

Table 5: Strengths and Limitations of Systematic Reviews and Meta-Analyses using AMSTAR[9]

Strengths	Limitations
Fareed, 2010[23]	
- Specific research question and hypothesis - Detailed description of included studies, except did not provide study designs of individual studies	- No reference to an a priori protocol - No description of extraction procedures, for example, whether two reviewers independently assessed the articles - Limited to English language and to PubMed search - Lacks critical appraisal of included studies, or assessment of potential for publication bias
Gowing, 2017[24]	
- Appropriate risk of bias assessment with overall GRADE quality of evidence for the primary outcomes - Comprehensive literature search (four databases, hand searching and conference proceedings) - Assessment of heterogeneity across studies using I2 - Detailed Characteristics of included and excluded studies	- Lacked a second reviewer, though all authors confirmed inclusion/exclusion of articles decided by one reviewer - Did not discuss potential for publication bias
Lobmaier, 2011[25]	
- Comprehensive search covering 7 databases - Independent screening by two authors	- Research question, population of interest, outcomes and comparators were not defined, and were vague (no specific PICO format), and no a priori protocol - No detailed information on study characteristics - No systematic critical appraisal - No comment on publication bias - Did not search for grey literature reports
Minozzi, 2011[26]	
- Clearly stated PICO research question and objectives - Comprehensive search strategy including three databases, trials protocol databases hand searching, conference proceedings, unpublished studies and investigator contacts - Three reviewers scanned titles/abstracts, and two reviewers extracted data - Risk of bias in studies, and publication bias, assessments complete	- Comparisons were underpowered, which authors attribute to high loss to follow up of oral naltrexone patients

Table 6 Strengths and Limitations of Randomized Controlled Trials using Downs and Black[10]

Strengths	Limitations
Coviello, 2010[17]	
- Detailed investigation of patient characteristics, including screening for depression, drug risk factors, and psychiatric disorders - Sensitivity analysis to account for missing data, i.e. imputation - Overall treatment groups were similar except control group had less heroin use in the last 30 days (1.9 versus 5.8 days), demonstrating successful randomization - Both ITT analysis and per-protocol estimates	- Un-blinded (no placebo in the control) - High drop-out rate, though similar across groups (1/3 of subjects completed six-month treatment) - Analysis may not have been appropriate (i.e. generalized estimating equations and Cox model) due to low sample sizes (n = 34)
Korthuis, 2017[18]	
- Allocation concealment achieved - Wash-out period of other opioid use agonist/antagonist treatment before study entry - ITT analysis - Low rate of non-consenting eligible participants (n=3/78 [4%])	- Open-label and only a pilot trial - Some evidence of unsuccessful randomization (31% vs 56% Female, 35% vs 16% White, 38% vs 52% disabled in control and treatment groups, respectively) - Only point estimates provided for secondary outcomes and only p-values provided for primary outcomes: underpowered study
Krupitksy, 2011[13]	
- Blinded investigators, staff, participants and sponsor to treatment allocation (used amber vials and syringes) at 13 sites - Allocation sequence concealment achieved - Power calculation suggests adequate power to detect clinically-important effect - Appropriate statistical analysis and redone by independent statistician - Successful randomization in terms of balance of characteristics	- Funding source, as well as actor that monitored the study, collected the data, and analysed the data, was pharmaceutical company Alkermes, which manufactures Vivitrol
Lee, 2015[22]	
- Recruitment involved electronic medical and jail release records screening - Allocation concealment achieved through shuffling of sealed envelopes by randomization block - ITT analysis to test 4 week differences in relapse -imputation of missing values based on i) assuming missing test is positive and ii) assuming last observed status for missing values - Successful randomization except slight higher homeless proportion in controls, higher employed proportion and younger age in treated group	- Open-label, non-blinded - Small sample size of 33 but still balanced characteristics - Short follow up (4 weeks) enabled 2 treatment doses - Low rates of follow up completion (10/17 [59%] in treatment group; 7/17 [41%] in control group) - Pilot study with very large confidence intervals
Lee, 2016[19]	
- Allocation concealment achieved through an independent	- Treatment was open-label and no placebo

Strengths	Limitations
automated telephone system - Sufficient power to detect effect with large sample size - Appropriate statistical analysis - Mainly successful randomization (past Heroin and any opioid use elevated in usual treatment group) - 77% follow up completed, and similar rate between treatment groups (79% for treatment vs 75% for control) suggesting minimal loss to follow up	- Highly motivated population participating because recruitment mainly through media rather than referrals (to avoid coercion), and inclusion criteria included a desire to use opiate-free treatment - May not be generalizable to criminal offender population due to recruitment method
Mitchell, 2012[14]	
- Double-blinded trial at 13 sites - Large sample size (n = 250) - Appropriate statistical analyses; outcome measured by treatment group	- Study author from Alkermes which may be a conflict of interest - Unclear outcome measures stated in methods - No information on randomization, allocation procedures or how blinding was achieved - described in another study - No table of characteristics of patients in each study arm to assess balance - Stated purpose was to study patients with chronic viral hepatitis or liver disease, but eligibility did not specifically include these patients
Mokri 2016[15]	
- Double-blinding with identical placebo treatment - Appropriate statistical analysis including ITT, between-group differences at follow up using survival analyses and analysis of variance - Successful randomization except slightly higher unemployed and married in treatment group (n=33 [65%] vs n=27 [53%], and n=16 [31%] vs n=11 [22%], respectively)	- No information to assess allocation concealment or randomization procedure
Otiashvili 2012[20]	
- Allocation concealment achieved through adaptive bias-coin randomization with urn design	- Comparator group did not receive behavioural therapy or have same opportunity to enter 14-day inpatient detoxification treatment, or receive $9US for negative urine samples, so cannot isolate effect of naltrexone separate from other drivers of successful outcome - Open-label - Analysis attempts limited by sparse data; 43% of follow-up assessments missing - Unsuccessful randomization (differences in HIV status; p = 0.009, sharing needles; p = 0.001, sharing syringes; p = 0.01)
Sullivan, 2013[16]	
- Appropriate analysis using time-to-event analysis to assess retention in treatment, and the interaction between type of treatment and urine toxicology, however unclear accounting for auto-correlation between repeat urine measures - Double-blinding, though unclear who exactly was blinded	- Methods of allocation concealment, randomization or blinding not described - Recruitment through word-of-mouth and advertising in newspapers may have limited the generalizability - No Table 1 to compare characteristics in the two arms - Nature of the placebo unclear

Strengths	Limitations
Sullivan, 2017[21]	
- Relevant research question about induction into oral naltrexone - Appropriate statistical model adjusting for other covariates such as primary type of opioid use at baseline, and auto-correlation between repeat observations - Some evidence of unsuccessful randomization (e.g. 14.3% vs 36.5% administered opioids intravenously in treatment vs control group respectively), however unbalanced covariates were adjusted for in the model	- Open-label RCT - Allocation procedure unclear - Comparison group not given standing adjuvant medications, so effect of these also inherently being tested in combination with XR-NTX - Unclear presentation of results (no table, standard errors or confidence intervals presented)

Table 7: Strengths and Limitations of Economic Studies using Drummond[11]

Strengths	Limitations
Baser, 2011[28]	
- Compared policy-relevant alternatives - Large sample size (14 million) and standard database - Costs derived from patient claims and several viewpoints of care considered - Propensity score matching and instrumental variable analyses used to ensure similarity of patient groups likely to receive different treatments	- The definition of the 'no medication' group, requires a claim for a nonpharmacological treatment, so those not actively seeking such treatment would be excluded - Limits the viewpoint to costs associated with care but not social costs of untreated opioid use disorders - No incremental cost effectiveness ratio considered or measure of effectiveness
Jackson, 2015[29]	
- Competing alternatives only were considered - Viewpoint was the state insurance payer; relevant for decision-making - Several costs considered, including drug costs, counseling, reimbursement costs for pharmaceuticals, monthly physician medication management - Sensitivity analysis to determine uncertain parameters	- Transition probabilities for XR-NTX were based on one clinical trial in Russia - Effectiveness measure limited to 'opioid-free days'
Murphy, 2017[6]	
- Based on an existing RCT comparing XR-NTX to treatment as usual - Costs considered were medical care visits, inpatient admissions, emergence department visits, mental health sessions, and criminal-justice related costs including visits to probation officers and direct costs of interactions with criminal justice system - Clinically-relevant effectiveness considered (time free from opioids)	- Cost estimations based on high-level averages, potentially limiting generalizability if costs vary - Based on 308 patients and one study - Assumptions not clearly stated
Ruger, 2012[27]	
- Based on existing RCT in Malaysia - Comprehensive collection of costs, including fixed costs of facilities, materials, and societal costs such as travel and family's time - Appropriate analysis and sensitivity analysis	- Short time horizon - Assumptions not clearly stated - Only based on 1 trial of 126 patients - Lack of detail on the study design and participating population

Table 8: Strengths and Limitations of Guidelines using AGREE II[12]

Strengths	Limitations
World Health Organization, 2009[32]	
- Scope and purpose of guidelines clearly stated - Evidence based on systematic reviews and clinical trials - Consulted group of technical experts to assess evidence using GRADE quality criteria - Drafts of guidelines circulated to organizations for feedback (external validity)	- No evidence of guideline evaluation or validation other than consultation with experts and other organizations - View of patients not explicitly considered
Kampman, 2015[30]	
- Formed independent committee with experts/researchers from several disciplines to oversee development, review treatments and help with writing - Draft guidelines sent to patient and caregiver groups, and other stakeholders (e.g. criminal justice system) for input, though only a 1-week period - Scope and purpose of guidelines clearly stated	- Patient/patient representative groups not included on guideline committee - Evaluation or validation unclear
Soyka, 2011[31]	
- Task force of worldwide experts in addition to systematic literature search - Grading of evidence quality based on study design and attributes such as blinding versus open-label	- No involvement of patients or community-based non-health professional stakeholders - Lack of detail on literature review methodology or synthesis
British Columbia Centre on Substance Abuse, 2017[8]	
- Developed using AGREE II framework - Independent funding (no pharmaceutical companies) - Representation from First Nations Health Authority, Corrections Services and Ministry of Health - Literature review and quality assessment	- No evident patient involvement - Lack of detail on literature review methodology or synthesis - Vague description of specific treatments and outcomes of interest
U.S. Department of Veterans Affairs, 2015[33]	
- Stringent standardized, and extensive, guideline development process involving multiple stages of consultation and interdisciplinary working group - Detailed description of methodology including systematic review and specific target population, interventions and outcomes of interest - Comprehensive systematic review - Large group of stakeholders and independent groups involved in development	- No evident patient involvement

Appendix 4: Main Study Findings and Author's Conclusions

Table 9: Summary of Findings of Included Studies

Main Study Findings	Author's Conclusion
Systematic Reviews	
Fareed, 2010[23]	
- Two studies (n=14 and n=272) assessing the heroin cravings among naltrexone patients, using a Visual Analogue Scale - One study (n=14) found naltrexone patients were "vulnerable to stress, drug cue-induced craving, and arousal responses,"(pg 338) potentially contributing to high relapse rates, while the other study (n=272) found abstinence is associated with less craving, independent of use of naltrexone.	"Two studies (23,24) explored the effect of opiate antagonist medication (naltrexone) on subjective and/or objective opiate craving. They reported that naltrexone did not reduce heroin craving." (pg 333)
Gowing, 2017[24]	
- Six studies assessed clinical outcomes associated with naltrexone treatment, mostly in combination with clonidine - Peak withdrawal severity was generally more severe when using the opioid antagonists rather than clonidine or lofexidine alone, though average severity may be less - The studies were too diverse to meta-analyze and overall the quality of evidence was poor	"The use of an opioid antagonist (naltrexone, naloxone or both) to induce withdrawal in combination with an alpha2-adrenergic agonist (clonidine or lofexidine) to ameliorate the signs and symptoms of withdrawal is a feasible approach to managing opioid withdrawal." (pg 22)
Lobmaier, 2011[25]	
- Sustained release naltrexone users use less opioids than those administered placebos, usual treatment or oral naltrexone (note that 'sustained release' combines both injection and implants) - Secondary outcomes including reduced hospitalizations for overdose or psychiatric reasons were also lower	"Currently available naltrexone injectable and implants have been shown to significantly reduce heroin use and alcohol consumption in patient populations." (pg 634)
Minozzi, 2011[26]	
Naltrexone versus placebo or no pharmacological treatment: Retention in treatment: RR = 1.18 (95% CI 0.72, 1.91) (Based on 2 studies; 88 participants) Retention and abstinence: RR = 1.43 (0.72, 2.82) (Based on 6 studies; 393 participants), though when restricted to studies with forced adherence (n = 230) RR = 2.93 (1.66, 5.18) Abstinence: RR = 1.39 (0.61, 3.17) (Based on 4 studies; 143 participants) Abstinence at follow up: RR = 1.28 (0.80,2.08) (Based on 3 studies; 116 participants) Side effects: RR = 1.29 (0.54, 3.11) (Based on 4 studies; 159 participants) Reincarceration: RR = 0.47 (0.26, 0.84) (Based on 2 studies; 86 participants) Naltrexone versus psychotherapy Abstinence at follow up: RR = 1.63 (0.62,4.26) (Based on 1 study; 38 participants)	"The findings of this review suggest that oral naltrexone did not performed better than treatment with placebo or no pharmacological treatments a part from the number of participants re-incarcerated during the study period. If oral naltrexone is compared with other pharmacological treatments such as benzodiazepine and buprenorphine, no statistically significant difference was found. The percentage of people retained in treatment in the include studies was low (28%)." (pg 12)

Main Study Findings	Author's Conclusion
Reincarceration: RR = 0.65 (0.26, 1.65) (Based on 1 study; 38 participants) Naltrexone plus psychotherapy versus benzodiazepines plus psychotherapy Retention and abstinence: RR = 1.67 (95% CI 0.96, 2.89) (Based on 1 study; 150 participants) Side effects: RR = 3.00 (0.63,14.36) (Based on 1 study; 150 participants) Naltrexone plus psychotherapy versus buprenorphine plus psychotherapy Retention and abstinence: RR = 0.37 (95%CI 0.13,1.08) (Based on 1 study; 87 participants) Overall study quality was low and most comparisons underpowered due to low participant numbers	
Randomized Controlled Trials	
Coviello, 2010[17]	
Oral naltrexone vs TAU - No significant group differences in treatment completion or attendance - No significant differences in positive opioid drug screens, use of heroin, other opioids, cocaine, alcohol, criminal charges, incarcerations, risky behaviours at six months, except the treatment group had more parole violations: n = 27/32 [84%] versus n= 7/31 [23%]; p = 0.043 - Significant group differences by linear (Wald c2(1)=7.18, p = 0.01) and quadratic (Wald c2(1)=3.92, p = 0.05) time effects. - Within-timepoint contrasts showed groups were not significantly different except between weeks 4 and 20 the naltrexone group had significantly lower opioid use	"Limited support for the use of oral naltrexone in the context of opioid-dependent parolee populations" (pg 10)
Korthuis, 2017[18]	
XR-NTX vs TAU Treatment initiation within 4 weeks of randomization: 42% (n=5/12) XR-NTX versus 100% (n=12/12) control; p = 0.002; the leading reason was inability to complete opioid detoxification Retention in counseling at 16 weeks: 100% (n=5/5) versus 40% (n=4/10); p = 0.04) Mean days of opioid use over past 30 days: -12.6 (n = 12) vs -13.2 (n = 12) Positive opioid screens at 16 weeks: -25% (n = 12) vs -16.7% (n = 12) Prescribed ART: +4% for both (92% to 96%; n = 25 and 96.2% to 100%; n = 26) % achieving HIV viral suppression: +1% vs +6.2% [80% (n=25) to 81% (n=21) vs 80.8% (n = 26) to 87.8% (n = 23)]	"The current study demonstrates that integration of XR-NTX into HIV clinics was feasible and safe for the treatment of OUD/AUD. These findings support the need for a multi-site trial to assess the capacity of integrated addiction treatment in HIV clinics to improve engagement and retention in the HIV care continuum." (pg 7)

Main Study Findings	Author's Conclusion
Krupitsky, 2011[13]	
XR-NTX vs placebo Proportion weeks confirmed abstinence: RD = 55 (95% CI 15.9, 76.1); p = 0.0002 Patients with total confirmed abstinence: RR = 1.58 (1.06, 2.36); p = 0.02 Proportion self-report opioid-free days: RR = 38.7 (3.3, 52.5); p = 0.0004 Craving (Visual Analogue Scale score): RD = –10·7 (–15.0, 6.4); p <0.0001 Number of days of retention: HR = 0.61 (0.44, 0.86); p = 0.0042 Positive naloxone challenge tests: RD = 1.3 (2.3 , 127.8); p <0.0001 Study completion: RR = 1·40 (1.06,1.85); p = 0.0171] HIV risky behaviour scores: RD = –0.057 (–0.113, –0.001); p= 0.0212 QoL scores (EuroQol-5D): RD = 11.4 (5.0, 17.8); p = 0.0005 Proportion 'much or very much improved 'on clinical global impression: RR = 1.49 (1.19, 1.87); p = 0.0002 Rates of adverse events resulting in discontinuation were similar in both groups.	"Detoxified, opioid-dependent adults voluntarily seeking treatment who received XR-NTX had more opioid-free weeks than those who received placebo. Efficacy did not vary by age, sex, or duration of opioid dependence" (pg 1511)
Lee, 2015[22]	
XR-NTX vs treatment as usual Primary outcomes Opioid relapse weeks 1-4: OR = 0.08 (95% CI 0.01, 0.48); p<0.004 Opioid relapse weeks 1–8: OR = 0.13 (0.02,0.78); p < 0.03) Confirmed opioid abstinence weeks 1-4: OR = 7.5 (1.3,44); p <0.03 Confirmed opioid abstinence weeks 1–8: OR = 16 (1.7,151); p< 0.007 % Opioid negative urine toxicologies weeks 1-4: OR = 3.5 (1.4,8.5); p<0.009 % Opioid negative urine toxicologies weeks 1–8: OR = 4.6 (2.1,10); p< 0.0001 Secondary outcomes Post-release injection drug use: 25% XR-NTX vs 6% controls Cocaine misuse: 56% vs 47% Participation in other community drug treatment: 19% vs 12% Re-incarceration rates: 31% vs 41% Adverse events: None	"In conclusion, in this pilot proof-of-concept randomized effectiveness trial XR-NTX was associated with lower opioid relapse rates among opioid-dependent adult males released from a large urban jail." (pg 1013)
Lee, 2016[19]	
XR-NTX vs treatment as usual Median time to relapse if occurred (weeks): HR = 0.49 (95% CI 0.36, 0.68); p < 0.001 % opioid relapse event: OR = 0.43 (0.28,0.65); p < 0.001 % 2-week intervals with abstinence OR = 2.50 (1.66, 3.76); p < 0.00 % opioid-negative urine samples: OR = 2.30 (1.48, 3.54); p < 0.001	"[This] U.S. multisite, open-label, randomized effectiveness trial showed that among adult offenders who had a history of opioid dependence, the rate of relapse was lower among participants assigned to extended-release naltrexone than among those assigned to usual treatment," though, "the prevention of opioid use by extended-release naltrexone did not persist through follow-up at week 52 and week 78." (pg 9)

Main Study Findings	Author's Conclusion
% days with self-reported opioid use: IDR = 0.35 (0.21, 0.59); p < 0.02 % days with cocaine use: IDR = 0.91 (0.56, 1.48); p = 0.71 Heavy drinking in past 30 days: OR = 0.89 (0.43, 1.87); p = 0.77 Any intravenous drug use: OR = 0.67 (0.25, 1.82); p = 0.43 Mean sexual risk score: RD = -0.11 ; p = 0.68 Any reincarceration: OR = 0.71 (0.33,1.52); p = 0.38 Total days of reincarceration: IDR = 0.63 (0.32,1.23); p = 0.22 Days incarcerated: RD = -6.5 (p = 0.1) Adverse events resulting in discontinuation: 3.3% treated vs 0% control	
Mitchell, 2012[14]	
XR-NTX vs placebo Median time to discontinuation from study: 96 days XR-NTX vs 168 days placebo (log rank test, p = .0042) ALT level: +3.8 IU/mL vs +6.2 IU/mL (not statistically significant) AST level: +4.2 vs +6.5 (not statistically significant) Mean GGT "declined slightly," (pg 994) in both groups (not statistically significant) Bilirubin level: +0.34 µmol/ml vs -1.84 µmol/ml (not statistically significant) Proportion with elevations greater than three times the upper limit of normal: ALT: n=21/107 (19.6%) vs n=11/85 (12.9%); p = 0.876 AST: n=15/107 (14.0%) vs n=9/85 (10.6%); p = 0.713 GGT: n=25/107 (23.4%) vs n=18/85 (21.2%); p = 0.811	"The results of the present study indicate that similar percentages of patients treated with XR-NTX developed elevations in AST, ALT, and GGT greater than three times the ULN." (pg 995)
Mokri, 2016[15]	
Oral naltrexone vs buprenorphine Mean days initial opioid abstinence: 28.8 (95% CI 20.0,37.5) vs 21.6 (14.4,28.7); p = 0.205 Mean days treatment retention: 70.6 (63.6,77.7) vs 56.5 (47.8,65.3); p = 0.013 Mean opioid negative urine tests: 19.7 (17.7, 21.6) vs 15.4 (13.1,17.8); p = 0.049 Proportion with sustained abstinence: n=8/51 (16%) vs n=4/51 (8%); p = 0.219 Completed 24 weeks of treatment: n=21/51 (41%) vs n=1/51 (2%); p < 0.001 Aggression, violence, impulsivity, self-injury or criminal justice involvement: 17/63 (27%) vs 22/66 (33%) ; p = 0.433 Died of drug overdose: 2/66[3%] vs 1/63 [2%] Protective transfer: 2/66 [3%] vs 3/63	"In this study, BNX compared to oral NTX was associated with a significantly greater number of opioid-negative urine tests (consistent with a greater total duration of verified opioid abstinence) and greater treatment retention, but not with significant differences on the primary outcome, initial duration of verified abstinence or the proportions with sustained, verified abstinence." (pg 879)
Otiashvili, 2012[20]	
Oral Naltrexone vs treatment as usual Entering detoxification: 0% vs 50% (n = 12/24); p < 0.001 Entering naltrexone treatment: n = 0/20 (0%) vs n=12/20 (60%); p< 0.001 Weekly positive urine samples: 8.4 (SE = 1.3) vs 5.1 (SE = 1.0); p = 0.43	"In this randomized controlled trial, participants assigned to a comprehensive intervention that paired behavioral treatment with naltrexone were significantly more likely than usual care participants to enter detoxification and naltrexone treatment, and provide significantly more opioid-negative urine samples." (pg 7)

Main Study Findings	Author's Conclusion
Weekly negative urine samples: 1.4 (SE =0.6) vs 7.0 (SE = 1.3); p < 0.001 Number of treatment sessions: 9.8 (SE = 1.6) vs 12.1 (SE = 1.8); p = .361 Number of urine samples collected 9.7 (SE = 1.6) vs 12.0 (SE = 1.8); p = .360	
Sullivan, 2013[16]	
XR-NTX vs Placebo Low-dose naltrexone: HR = 0.15 (SE of log coefficient = 0.70, p =0.075) Low-dose naltrexone-positive urine toxicology interaction: HR = 9.21 (SE of log coefficient = 0.89, p =0.013) High-dose naltrexone: HR = 0.09 (SE of log coefficient = 0.81, p =0.0028) High -dose naltrexone-positive urine toxicology interaction: HR = 3.93 (SE of log coefficient =1.07, p =0.2)	"Opiate-positive urines predicted subsequent dropout from treatment in the placebo group and the low dose-192mg naltrexone group, while in the high-dose-384mg naltrexone condition, opiate-positive urines were less likely to lead to dropout; rather, in the high-dose naltrexone group patients tended to produce only one or a few positive urines, then achieve sustained abstinence. This finding is consistent with the expected mechanism of extinction through repeated trials of opiate use that are blocked by naltrexone--"testing the blockade."" (pg 6)
Sullivan, 2017[21]	
Oral Naltrexone-assisted vs buprenorphine-assisted detoxification Successful XR-NTX induction: OR = 2.89; p = 0.01 Second XR-NTX injection week 5:OR = 2.78; p = 0.040) Secondary outcomes: No difference between treatment arms (Based in Figure 2A and 2B pg 264) for daily presence of mild withdrawal, moderate-severe withdrawal, continuous measure of opioid withdrawal in weeks 2-5 or depression scale rating Completing 8-day detoxification: 56.1% (N=55) treatment vs 46.2% control (N=24) (not significant) % 2-week abstinence at week 5 after XR-NTX induction: 78.2% (N=43) in treatment vs 88.2% (N=15) control Adverse events: No significant difference in the proportion of reported adverse events between groups	"We found that participants undergoing a rapid 8-day, naltrexone-assisted treatment were significantly more likely to successfully initiate XR-naltrexone than participants assigned to the standard 15-day method that includes 7 days of buprenorphine taper." (pg 464)
Economic Studies	
Baser, 2011[28]	
- 6-month total cost including inpatient, outpatient, and pharmacy costs was $10,710 per patient in the any medication group compared with $6791 per patient in the no medication group. - 6-month costs per patient for detoxification and/or rehabilitation admissions ($205 vs $2083) and opioid-related ($381 vs $1823) and non–opioid related ($2928 vs $4184) admissions were significantly lower compared with those not receiving medication. - For outpatient services, overall healthcare cost savings were $4161 per patient treated with medication relative to those not receiving medication ($10,192 vs $14,353). - The overall healthcare costs for patients given XR-NTX were not different from those given buprenorphine, and the overall	- The cost of XR-NTX was ten times that of methadone, but the total healthcare costs associated with XR-NTX were half those associated with methadone. - The overall healthcare costs were not significantly different than those associated with buprenorphine

Main Study Findings	Author's Conclusion
healthcare costs per patient in the group treated with methadone were significantly greater than those with XR-NTX ($16,752 vs $8582, respectively), due to greater healthcare usage	
Jackson, 2015[29]	
- Patients expected to be abstinent for approximately 56, 49, and 96 days when treated with MMT, BMT and XR-NTX respectively - XR-NXT has the highest days of treatment but was more effective to discourage opioid use during treatment (6% of treatment time spent using opioids versus 45% and 47% on BMT and MMT respectively) - It would cost the payer an additional $72 to gain one additional opioid-free day relative to MMT - There was a general lack of evidence on XR-NTX effectiveness in the U.S., thus making this parameter the most uncertain	"Our base case results suggest that XR-NTX is cost-effective if state health payers are willing to pay at least $72 per opioid-free day gained, about the cost of treating three patients with methadone for one day." (pg 5)
Murphy, 2017[6]	
25 weeks: Total incremental cost = 3243 (SE = 703) p < 0.001) QALYs = 0.04 (0.02) 0.02; Cost per QALY = 162150 Abstinent years = 0.14 (0.03) p<0.001 Cost per abstinent year = 46 329 78 weeks: Total incremental cost = 2292 (SE = 1081) p = 0.03) QALYs = 0.02 (0.02) p = 0.25 Cost per QALY = 76 400 Abstinent years = 0.09 (0.03) p = 0.004 Cost per abstinent year = 16 371 No significant differences in the cost associated with criminal justice resource utilization	"With an incremental average direct cost of $3243, the 25-week XR-NTX intervention was significantly more expensive than TAU, even after accounting for potential cost-offsets associated with other forms of opioid use disorder therapy and non-study health-care services, both of which were lower for XR-NTX versus TAU participants, but did not reach statistical significance at the 5% level." (pg 7)
Ruger, 2012[27]	
Cost per additional day (ICER): in treatment Naltrexone vs Placebo: 20.53 Buprenorphine vs Naltrexone: 21.19 in treatment without heroin use Naltrexone vs Placebo: 47.89 Buprenorphine vs Naltrexone: 25.89 In treatment without heroin relapse Naltrexone vs Placebo: 11.49 Buprenorphine vs Naltrexone: 46.1 Maximum consecutive days absent Naltrexone vs Placebo: 15.96 Buprenorphine vs Naltrexone: 41.12 Cost per additional unit of outcome achieved (6 month outcomes) Percent reporting injection drug use Naltrexone vs Placebo: Dominated Buprenorphine vs Naltrexone: 18,931.40	"Buprenorphine was more effective and more costly for all primary and most secondary outcomes compared to naltrexone. Incremental cost-effectiveness ratios were small – below $50 for primary outcomes, mostly below $350 for secondary outcomes. Naltrexone was dominated by placebo for all secondary outcomes" (pg 7)

Main Study Findings	Author's Conclusion
Treatment retention: Naltrexone vs Placebo: Dominated Buprenorphine vs Naltrexone: 87.39 Number remaining in treatment without relapsing Naltrexone vs Placebo: Dominated Buprenorphine vs Naltrexone: 116.52 Number still abstinent from illicit opiates Naltrexone vs Placebo: Dominated Buprenorphine vs Naltrexone:233.04 AIDS Risk Inventory total score Naltrexone vs Placebo: Dominated Buprenorphine vs Naltrexone: Dominated Days of outpatient treatment for alcohol or drugs, past 30 days Naltrexone vs Placebo: 56.03 Buprenorphine vs Naltrexone: D Days experiencing medical problems, past 30 days Naltrexone vs Placebo: Dominated Buprenorphine vs Naltrexone: 617.75 Days paid for working, past 30 days Naltrexone vs Placebo: 77.14 Buprenorphine vs Naltrexone: Dominated Malaysian Ringgit earned from employment, past 30 days Naltrexone vs Placebo: Dominated Buprenorphine vs Naltrexone: 1.57 Malaysian Ringgit received from mate, family, friends, past 30 days Naltrexone vs Placebo: 3.29 Buprenorphine vs Naltrexone: 21.68 Malaysian Ringgit illegally received, past 30 days Naltrexone vs Placebo: Dominated Buprenorphine vs Naltrexone: 1.81	
Guidelines	
World Health Organization, 2009[32]	
'Strong' recommendation based on low to moderate quality evidence that (pg xviii) i) "For the pharmacological treatment of opioid dependence, clinicians should offer opioid withdrawal, opioid agonist maintenance and opioid antagonist (naltrexone) treatment, but most patients should be advised to use opioid agonist maintenance treatment." 'Standard' recommendation based on low quality evidence that (pg xviii) ii) "For opioid-dependent patients not commencing opioid agonist maintenance treatment, consider antagonist pharmacotherapy using naltrexone following the completion of opioid withdrawal."	"Pharmacological treatment options should consist of both methadone and buprenorphine for opioid agonist maintenance and opioid withdrawal, alpha-2 adrenergic agonists for opioid withdrawal, naltrexone for relapse prevention, and naloxone for the treatment of overdose." (pg xiv)
Kampman, 2015[30]	
- Naltrexone is recommended to prevent relapse in opioid use disorder; oral naltrexone (daily 50 mg or 100mg 2x weekly plus 150 mg dose once weekly) could be considered when adherence can be supervised, otherwise XR-NTX (380mg	"At this point in time, the available evidence indicates that use of medications in addition to psychosocial treatments is supported for the treatment of opioid use disorder." (pg 367)

Main Study Findings	Author's Conclusion
every 4 week) - "The use of combinations of buprenorphine and low doses of oral naltrexone to manage withdrawal and facilitate the accelerated introduction of extended-release injectable naltrexone has shown promise. More research will be needed before this can be accepted as standard practice." (pg 362) - Psychosocial treatment should be given in conjunction with XR-NTX as its efficacy has not been confirmed without it - Although methadone, buprenorphine, and naltrexone are all superior to no treatment in opioid use disorder, less is known about their relative advantages	
Sokya, 2011[31]	
"Limited Positive Evidence from Controlled studies" (pg 163) to use oral naltrexone 50 mg to treat abuse and dependence "Inconsistent Results" (pg 163) to use naltrexone under general anesthesia (dose not stated) to treat withdrawal Recommendation: "Oral naltrexone is not a first line treatment for opioid dependence (1). However, oral naltrexone might be effective in a small subgroup of highly motivated and well-integrated patients (3). Retention in naltrexone treatment is usually poor." (pg 172) Recommendation: "Although depot naltrexone is now approved and available in the United States for the treatment of opioid dependence, additional studies are needed to define more clearly its clinical efficacy over the long term" (pg 173)	N/A
British Columba Centre on Substance Abuse, 2017[8]	
"For individuals with a successful and sustained response to agonist treatment desiring medication cessation, consider slow taper (e.g., 12 months). Transition to oral naltrexone could be considered upon cessation of opioids." (Medium quality of evidence; Strong Recommendation) (pg 13) "For patients wishing to avoid long-term opioid agonist treatment, provide supervised slow (> 1 month) outpatient or residential opioid agonist taper rather than rapid (< 1 week) inpatient opioid agonist taper. During withdrawal management, patients should be transitioned to long-term addiction treatment to prevent relapse and associated harms. Oral naltrexone can also be considered as an adjunct upon cessation of opioid use" (Low quality of evidence; weak recommendation) (pg 13)	N/A
U.S. Department of Veterans Affairs, 2015[33]	
"For patients with opioid use disorder for whom opioid agonist treatment is contraindicated, unacceptable, unavailable, or discontinued and who have established abstinence for a sufficient period of time (see narrative), we recommend offering: Extended-release injectable naltrexone" (Strong recommendation with moderate quality evidence) (pg 38) "Based on the available evidence, oral naltrexone cannot be recommended for treatment of opioid use disorder" (pg 43)	N/A

XR-NTX = extended release injectable naltrexone; BMT = Buprenorphine maintenance treatment; MMT = Methadone maintenance treatment; OR = odds ratio; HR = hazard ratio; RD = relative difference; RR = risk ratio; QoL = quality of life; IDR = incidence density ration; 95% CI = 95% confidence interval; SE = standard error; QALY = quality-adjusted life year ; AST = aminotransferase; ALT =alanine aminotransferase; GGT = gamma-glutamyl aminotransferase